# Indian Institute of Science

## Centre for BioSystems Science and Engineering

## BSSE Seminar

**6th January 2020 (Monday), 4:00 PM, MRDG Seminar Hall, 1st floor, Biological Sciences Building**

# A New Approach to Metabolism: The Power of a Good 'RACIPE'


## Dr. Dongya Jia

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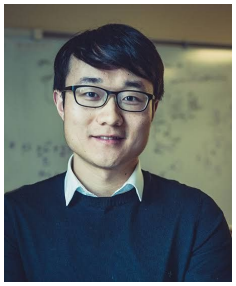
**ABOUT THE SPEAKER**



Dongya Jia completed his bachelor's degree in Systems Biology at the University of Science and Technology in China in 2013. He then joined the group of Prof. Herbert Levine at Rice University and received his Ph.D. in Systems/Synthetic/Physical Biology in 2018. He then was appointed as a research fellow on the CPRIT-funded Computational Cancer Biology Training Program. Dongya Jia's research interest is using systems biology approaches to uncover the principles underlying the phenotypic plasticity and cell-fate decision making in cancer. Specifically, he integrates mathematical modeling and data analysis to elucidate the emergent dynamics of cellular networks governing metastasis and cancer metabolism.

**ABSTRACT**


Metabolic plasticity allows cells to adjust their metabolic phenotypes. Both glycolysis and oxidative phosphorylation (OXPHOS) can be adapted by cells to meet their bioenergetic and biosynthetic requirements in a context-dependent manner. Despite the advance in studies focusing only on glycolysis or OXPHOS, it remains largely unknown how cells orchestrate different metabolic phenotypes. To address this question, there is an urgent need to develop systemic approaches to quantitatively study the interplay between glycolysis and OXPHOS. Mathematical modeling approaches have been employed to elucidate metabolic plasticity. These approaches offer a quantitative and dynamical perspective of metabolism mostly focusing on either metabolic pathways or gene activities. However, the alteration of the metabolic activity is often coupled with the change in gene activity, and vice versa. Thus, to comprehensively characterize metabolism, a modeling framework integrating gene regulation with metabolic pathways is needed. Here, we establish a theoretical framework to elucidate metabolic decision-making by coupling gene regulation with metabolic pathways. After an extensive literature search, we construct a regulatory network of metabolism featuring regulations by both genes and metabolites. To identify the robust dynamical features of the regulatory network, we utilize a variation of our previously developed computational method called RAndom CIrcuit PErturbation (RACIPE). The overall strategy involves randomizing the modeling parameters for each simulation and collecting all stable steady solutions for statistical analysis, by which the most significant solution patterns can be identified. Our modeling results demonstrate a direct association between the activities of AMPK and HIF-1, master regulators of OXPHOS and glycolysis, respectively, with the activities of three major metabolic pathways: glucose oxidation, glycolysis and fatty acid oxidation (FAO). Our modeling results indicate that in addition to glycolysis and OXPHOS, cells can acquire two additional metabolic phenotypes - a hybrid metabolic phenotype where cells actively use both glycolysis and OXPHOS and a metabolically inactive phenotype where cells exhibit low activity of both glycolysis and OXPHOS. We verify the model prediction using metabolomics and transcriptomics data from paired tumor and adjacent benign tissue samples from a cohort of breast cancer patients and RNA-sequencing data from The Cancer Genome Atlas and Gene Expression Omnibus. We further validate the model prediction by in vitro studies of aggressive triple-negative breast cancer (TNBC) cells and BRAF-mutated melanoma cells. In summary, our work serves as a platform to symmetrically study cellular metabolic plasticity by modulating both genes and metabolic pathways, through integrating mathematical modeling, data analysis with experiments.